REMARKS

The specification is amended to correct a repeated typographical error.

The pending claims 50-55, 60 and 62-66 were removed and new claims 67 to 79 are introduced. This manner of amendment was chosen for its editorial simplicity. No new matter is added by any amendment.

The new claim 67 recites that the docetaxel used is "free from ethanol". Support for this term is found in the specification at, e.g. page 9, lines 10-14.

Restriction

The Examiner has restricted the subject matter of the examination to processes in which ethanol is used as the solvent (i.e. claim 71). Applicants respectfully traverse this requirement once again.

With respect to the new claims, claim 71 recites the elected species of solvent. All other claims except claim 72 are generic with respect to the species of solvent.

Applicants reiterate that the present invention is unitary and that election of species practice with respect to the selection of solvents used in steps a)(i) and a)(ii) is appropriate. The Examiner asserts that she has applied a reference that removes the technical feature deemed to unify the claims from consideration as present in the prior art. Applicants disagree.

The claims in their present form emphasize the steps of the process, which are not disclosed in the prior art and which result in stabilized solutions of docetaxel. In particular, the Applicants have found that degradation of docetaxel occurs in the solutions of the prior art. The present inventors have found that such degradation occurs due to ethanol being present in the composition, and this is not recognized in the prior art.

Accordingly, the present claims recited that a docetaxel material is prepared having a very low (i.e. below 0.12% by weight) water content and being free of ethanol. That docetaxel material is then added to an acidified surfactant. Neither of the removal of water nor of ethanol

is described by the cited references, nor is the use of an acidified surfactant. Neither is addition of dried docetaxel to an acidified surfactant described.

Bastart '582 discloses addition of an ethanol solution of docetaxel to a surfactant. This is precisely counter to the present invention, in which docetaxel is first dried, and then dry, solid docetaxel that is free of ethanol is added to acidified polysorbate (see, claim 67). Chi '249 discloses that docetaxel may be "anhydrous", but may also be a hydrate. Nothing in Chi '249 discloses or suggests the process that is presently claimed. Sharma '720 discloses only processes for recrystallizing docetaxel and paclitaxel. Again the reference provides no teaching about formulation at all. Zeldis '726 discloses formulations of thalidomide, and never even mentions docetaxel.

Not one of the references cited by the Examiner is in fact novelty-destroying of the invention nor makes the present invention obvious. Accordingly, the unity of the invention must be acknowledged and the examination conducted under election of species practice with respect to the selection of solvent in step a) and starting material, as urged previously by the Applicants.

Claim Rejections - 35 USC § 112

Claism 50-55, 60 and 62-66 are rejected under 35 USC § 112, second paragraph as allegedly being indefinite. In particular, the Examiner asserts that it is unclear whether the pH stated in the claims relates to the excipient alone or to the pharmaceutical composition as a whole after the formulation is completed.

New claim 67 clearly recites that the pH of the surfactant is adjusted. New claim 77 recites that the pH of the completed pharmaceutical composition is adjusted. Thus, the instant rejection is obviated.

The Examiner also asserts a lack of antecedent basis for the term "the acid" in claims 64-66. This problem has been addressed in the amended claims; new claim 67 recites "an acid" providing the necessary antecedent basis.

Claim Rejections - 35 USC § 102

Claims 50, 60 and 62-63 are rejected under 35 USC § 102(b) as being anticipated by Bastart '582. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

As explained above, Bastart '582 discloses the addition of a surfactant to an ethanol solution of docetaxel. This is quite a different process from that recited in the present claims, and accordingly, claims 67-79 should be found free of the present rejection.

Claim Rejections - 35 USC § 103

Claims 50, 60 and 62-63 are rejected under 35 USC § 103(a) as obvious over Chi '249. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The present invention, as now recited in claim 67, is a process in which a dried form of docetaxel is dissolved in an acidified polysorbate surfactant. Chi '249 does disclose that docetaxel may be "anhydrous", but also that it may occur in hydrated forms. Absolutely nothing in Chi '249 discloses or suggests the process steps recited in the present claim 67. Accordingly, the present claims 67-79 are **not** *prima facie* obvious in view of the cited reference and the instant rejection must be withdrawn.

Claims 51-55 stand rejected under 35 USC § 103(a) as being obvious over Bastart '582 in view of Sharma '720. This rejection is respectfully traversed as applied to the present claims. Reconsideration and withdrawal thereof are requested.

Applicants submit that the Examiner fails to establish *prima facie* obviousness of the claimed invention. As explained above, Bastart '582 does not disclose or suggest **any** of the steps of the presently claimed process; indeed the reference teaches a process that, as it uses ethanol to dissolve the docetaxel, is completely counter to the present invention and would destroy the advantage of the instant invention, which is obtained by eliminating ethanol from the product (which occurs during the azeotropic distillation; see, *e.g.* Example 2 beginning on page 21).

Sharma '720 discloses nothing that remedies the deficiencies of Bastart '582. As explained above, Sharma '720 discloses only recrystalization processes. Furthermore, Sharma '720 in fact teaches away from the present invention, by actually urging that the hydrated docetaxel is preferable and provides a more stable solution. See, *e.g.* paragraph [0004]:

> **[0004] Similarly paclitaxel trihydrate is reported to have markedly superior stability in comparison to the anhydrous product. (Authelin el al U.S. Pat. No. 6,002, 022). According to this invention, paclitaxel trihydrate is obtained from a mixture of water and an aliphatic alcohol containing upto three carbon atoms, specifically methanol. The water/alcohol weight ratio used in this process is between 3/1 to 1/3. The crystals, thus obtained, are dried at about 40° C. under reduced pressure.**

Accordingly, the combination of Bastart with Sharma fails to disclose or suggest each and every element of the presently claimed invention, and furthermore combining the references in the manner suggested by the Examiner would urge the artisan to utilize a hydrated docetaxel, completely contrary to the drying steps a)(i) and a)(ii) in the present claims.

Thus, the present invention is not *prima facie* obvious in view of the combination of Bastart and Sharma and the instant rejection must not be applied to the present claims.

Claims 64-66 are rejected under 35 USC § 103(a) as being unpatentable over Bastart '582 in view of Zeldis '726. This rejection is respectfully traversed as applied to the present claims. Reconsideration and withdrawal thereof are requested.

As explained above, Bastart '582 in fact discloses an invention counter to the presently claimed invention. Zeldis '726 speaks only about thalidomide and thus fails entirely to say anything relevant to the present invention, which relates to docetaxel, a completely different compound that would have entirely different properties, including susceptibility to stabilization by acidification.

Indeed, Zeldis '726 discloses that ethanol should be used as a vehicle for a pharmaceutical composition (of thalidomide), at col. 24, lines 7 ff. ("water miscible vehicles such as, ..."):

> Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Such is in contradistinction to the present invention, which seeks to avoid the use of ethanol.

Thus, the presently claimed invention is **not** *prima facie* obvious over the combination of Bastart and Zeldis and the instant rejection should not be applied to the present claims.

Should there be any outstanding matters that need to be solved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell, Ph.D., Reg. No. 36,623, at the telephone number of the undersigned bellow, to conduct an interview in an effort to expedite prosecution in the connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.R.F. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

By _____

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